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(54) PRODUCTION OF SOLID PREPARATIONS CONTAINING CARBOCHROMENE HYDROCHLORIDE

(71) We, CASSELLA FARBWERKE MAINKUR AKTIENGESELLSCHAFT 526, Hanauer Landstrasse, 6 Frankfurt (Main)-Fechenheim, Germany, a body corporate organised under the laws of Germany, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to the production of solid preparations containing carbochromene hydrochloride. Medicinal preparations as just mentioned are at present produced either as soft gelatin capsules or as dragées. The soft gelatin capsules contain an oily suspension of the active compound (i.e. carbochromene hydrochloride) and are found to be unstable in tests at elevated temperature, as too are dragées containing carbochromene hydrochloride. This instability can be attributed to the active compound being gradually decomposed hydrolytically under the influence of moisture and elevated temperature. This has had the consequence that when, for example, the previously known preparations containing carbochromene hydrochloride have had to be despatched for use in the tropics, it has been necessary to take quite exceptional precautions in packing them, to prevent the active compound being damaged by hydrolysis.

It has also been a disadvantage that a considerable technical effort has been required to protect the personnel operating the processing equipment used, since carbochromene hydrochloride, when it acts externally, has skin-irritant properties which lead to certain allergies. Thus, when the dragées have been produced by granulating a starting material made moist with alcohol, special measures have been necessary for protection against dust and explosion and for preventing contamination of the environment.

It may be mentioned here that, upon the administration of the forms of carbochromene hydrochloride which have hitherto been used for peroral administration, the adsorption of the active compound has taken place in the upper and middle portions of the small intestine.

Accordingly, there has been a need for a process by which carbochromene hydrochloride can be processed in a simple manner to provide solid preparations which remain stable even under the influence of moisture and warmth and which have optimal properties for therapy.

According to the present invention, we provide a process for the production of a solid preparation containing carbochromene hydrochloride, wherein carbochromene hydrochloride together with based on the weight of the carbochromene hydrochloride, 1—30% by weight of filler, 1—20% by weight of swelling and disintegrating agent, 1—10% by weight of flowing and loosening agent, and 10—50% by weight of melting aid are submitted to heating and to intermixing at a temperature in the softening range or melting range of the melting aid, until granules are formed therefrom.

In a process according to the invention, we prefer to use, based on the weight of the carbochromene hydrochloride, 2—20% by weight of filler and/or 2—10% by weight of swelling and disintegrating agent and/or 2—8% by weight of flowing and loosening agent and/or 15—30% by weight of melting aid.

The granules initially formed may if desired be broken down, with a view to their being administered in this form or processed into solid forms for peroral administration, for example capsules, tablets or dragées. The breaking down of the granules may appropriately be carried out while the granules are still in a plastic condition. The granules can

still be warm, or can still be cooling, or can have already cooled. In this breaking down, individual granule particles themselves are not broken, but larger bodies comprising a number of granule particles agglomerated with one another or adhering to one another at their points of contact are disintegrated to give individual granule particles. This breaking down may for example be effected on vibrating or oscillating sieves. If desired, a classification (according to particle size, that is) can follow this breaking down, or can be performed concurrently therewith. However, this classification is not necessary in most cases inasmuch as the individual granule particles resulting from the breaking down are mostly of a sufficiently uniform size.

The breaking down of the granules initially formed is not necessary if care is taken to ensure that granule particles do not agglomerate to form larger bodies. This can be achieved, for example, by judicious termination of the mixing operation and/or the supply of heat.

The granules produced can be utilised in solid form for the peroral administration of carbochromene hydrochloride either as produced or, if desired, after breaking down and classification of granule agglomerates.

It is also possible, however, for the granules to be processed into other solid forms for administration; for example, they may be made into capsules, tablets or dragées. For this purpose it is generally appropriate additionally to admix with the granules 1—10% by weight (preferably 2—5% by weight) of a swelling and disintegrating agent, and/or 1—15% by weight (preferably 2—10% by weight) of a flowing and loosening agent and/or mould release agent and lubricant. The resulting mixture may, for example, be put into capsules or made into tablets, which may, for example, be single-layer tablets, multilayer tablets or dry-coated tablets, or again made into cores for film-coated or sugar-coated tablets.

In a process according to the invention it is not necessary that the carbochromene hydrochloride, filler, swelling and disintegrating agent, flowing and loosening agent and melting aid should be heated to a temperature so high that the melting aid, or even the entire mixture, has completely melted. Thus in accordance with the invention, the composition has only to be heated, while being mixed, until the melting aid (this being a material which does not have a sharp melting point, but has a softening range or melting range) reaches its softening range or melting range.

The melting aid used in accordance with the invention serves the purposes of enabling or facilitating the formation of the granules, and of controlling the hydrophilic-lipophilic properties of the preparation which is finally produced. The melting aids which we contemplate generally have melting ranges or softening ranges between 40°C and 100°C, preferably between 55°C and 85°C. Examples of suitable melting aids are: hydrogenated oils, e.g. hydrogenated castor oil, hydrogenated coconut oil, hydrogenated groundnut oil; esters, especially mono-, di- and tri-glycerides of fatty acids, e.g. glyceryl mono-stearate/palmitate, glyceryl tri-stearate/palmitate, self-emulsifying glyceryl mono/di-stearate, glyceryl mono/di/tri-stearate/palmitate, and esters of purified montan wax acids, for instance Hoechst Wax E ("Hoechst is a registered Trade Mark); higher fatty acids or wax acids, e.g. stearic acid, palmitic acid, behenic acid, myristic acid and purified montan wax acids, for instance Hoechst Wax S; higher fatty alcohols, e.g. lauryl alcohol, 12-hydroxystearyl alcohol, cetyl alcohol, stearyl alcohol, myristyl alcohol, myricyl alcohol, arachidyl alcohol, carnaubyl alcohol and ceryl alcohol; and natural, partly synthetic and wholly synthetic waxes, e.g. beeswax, carnauba wax, paraffin wax, vaseline wax, ozokerite, ceresine, spermaceti, solid polyethylene glycols, and polyethylene having a low softening point, for example Hoechst Wax PA 250.

The following are preferably used as melting aids: purified montan wax acid esters, e.g. Hoechst Wax E. purified montan wax acids, e.g. Hoechst Wax S, carnauba wax, hydrogenated castor oil, glyceryl mono/di/tri-stearate/palmitate, and polyethylene glycols having average molecular weight of 4,000—20,000.

The fillers used in accordance with the invention serve to increase the mass of the preparation and in certain cases they also make it possible to influence the dissolving characteristics and the pH and ionisation characteristics of the preparations. Examples of suitable fillers are: calcium hydrogen phosphate dihydrate, calcium tri-phosphate, calcium sulphate dihydrate, sodium carbonate, sodium bicarbonate, calcium carbonate, magnesium carbonate, ammonium chloride, citric acid, tartaric acid, lactose, sucrose, mannitol, kaolin, diatomaceous earth, cellulose and microcrystalline cellulose. Calcium hydrogen phosphate dihydrate, calcium sulphate dihydrate or lactose are preferably used as fillers.

The swelling and disintegrating agents used serve the purpose of controlling the disintegration characteristics of the preparation. Examples of suitable swelling and disintegrating agents are: starch (rice starch, maize starch, potato starch and various other kinds), sodium amylopectin glycollate (ultra-amylopectin), methylcelluloses, isopropylmethylcelluloses, methylhydroxyethylcelluloses, hydroxypropylcelluloses, hydroxyethylcelluloses, hydroxypropylmethylcelluloses, carboxymethylcelluloses and salts and esters thereof, alginic acids and salts and esters thereof, polyacrylic acids

and salts and esters thereof, guar gum, carrageen, carboxymethyldextrans and sodium carboxymethylstarch. The agents which we prefer, however, are: starch, sodium amylopectin glycollate (ultra-amylopectin) and methylhydroxyethylcelluloses and sodium carboxymethylcelluloses having a viscosity of 500—1,500 cP, sodium carboxymethyl-starch and crosslinked polyvinylpyrrolidone.

The flowing and loosening agents used serve the purposes of controlling the mixing behaviour of the composition during the granule-forming process, and of controlling the porosity of the granules. Examples of suitable flowing and loosening agents are: colloidally dispersed silicic acid, e.g. Aerosil 200 ("Aerosil" is a registered Trade Mark), colloidally dispersed hydrophobic silicic acid, e.g. Aerosil R 972, and amorphous silicic acids, e.g. Syloid (various grades: "Syloid" is a registered Trade Mark). Colloidally dispersed (optionally hydrophobic) silicic acid is a preferred agent.

Mould release agents and/or lubricants may optionally be used in a process according to the present invention; they may if necessary be used together with flowing and loosening agents of the kind already mentioned, in the further processing of the resulting granules. Examples of suitable mould release agents and lubricants are magnesium stearate, calcium stearate, zinc stearate, aluminium stearate, calcium behenate, talc and silicone oil. Magnesium stearate is preferably used as the mould release agent and lubricant.

The active compound carbochromene hydrochloride can also be combined with other pharmaceutically active substances, for example with digoxin, α-methyldigoxin, Cymarin, Nifenalol, Hydroxyzin, nicotinic acid and salts and esters thereof, clofibric acid and salts and esters thereof, xanthines and xanthine derivatives, pyridine-3-carbinol, dihydroergotamine tartrate, potassium chloride, Rauwolfia alkaloids, thiabutazide, Clofenamid, Hydralazin theophyllinate, phenobarbital, Prenylamin, Dipyridamol, nitroglycerin, pentaerythritol tetranitrate and chlorodiazepoxide hydrochloride.

Substances approved by Public Health authorities are used as auxiliaries, that is to say as fillers, swelling and disintegrating agents, flowing and loosening agents, melting aids and mould release agents and lubricants.

Not merely a single melting aid, but a mixture of two or more melting aids, is generally used. In the case of the other groups of auxiliary substances, it is also possible to use mixtures, that is to say, for example, a mixture of various swelling and disintegrating agents or a mixture of various flowing and loosening agents.

The percentages quoted relate to the total mixture present in each case.

The availability of the active compound in the gastrointestinal tract can be controlled in a manner which is optimal for therapy by means of a suitable qualitative and quantitative selection in the hydrophilic-lipophilic composition of the melting aid, together with a suitable qualitative and quantitative selection of the fillers, swelling and disintegrating agents, flowing and loosening agents, and mould release agents and lubricants. If, for example, a melting aid or a mixture of melting aids with predominantly lipophilic properties is used, the liberation of the active compound is delayed, while when using a melting aid or a mixture of melting aids with predominantly hydrophilic properties, the release of the active compound takes place more quickly.

The porosity of the resulting granules can be controlled, and the penetration of liquid can be accelerated or delayed, by means of a suitable qualitative and quantitative selection of the loosening agents.

By means of a suitable qualitative and quantitative selection of the swelling and disintegrating agents, which swell and disintegrate more slowly in the acid regions of the gastrointestinal tract than in regions of higher pH-values, it is possible to delay release of the active compound in the acid regions.

The ionisation conditions in the gastro-intestinal tract can be influenced by means of a suitable qualitative and quantitative selection of the fillers.

If the process according to the invention is carried out suitably, particularly by means of a suitable selection of the auxiliary substances, it is possible both to accelerate and to delay the availability of the active compound carbochromene hydrochloride in comparison with the form commercially available hitherto, soft gelatin capsules.

Forms for administration which have an accelerated release of the active compound can be obtained if melting aids having predominantly hydrophilic properties, for example polyethylene glycols, are used and/or colloidally dispersed silicic acid or amorphous silica is used as the flowing and release agent and/or starch (rice starch, maize starch, potato starch and the like), sodium amylopectin glycollate, sodium carboxymethyl starch or crosslinked polyvinylpyrrolidone is used as the swelling and disintegrating agent.

Forms for administration which have delayed release of the active compound can be obtained if melting aids with predominantly lipophilic properties, for example montan wax acids, montan wax acid esters, carnauba wax or glyceryl mono/di/tristearate/palmitate are used and/or colloidally dispersed hydrophobic silica is used as the flowing and loosening agent and/or a sodium carboxymethylcellulose, methylcellulose, methylhydroxyethylcellulose or hydroxypropylmethylcellulose is used as the swelling and disintegrating agent.

The resorption of the active compound in

the various sections of the gastro-intestinal tract can be controlled by means of the possibilities indicated.

The granules containing carbochromene hydrochloride which have been manufactured and compounded in accordance with the invention, mixtures thereof and the forms for administration prepared from them have the advantage, compared with the products prepared by processes available hitherto, that the unpleasant properties which arise when carbochromene hydrochloride acts externally, have disappeared to the extent that processing becomes possible without special precautionary measures.

In contrast to the customary methods of manufacture involving dry granulation and moist granulation with subsequent drying, evolution of dust can be largely avoided, especially if the granules are, if appropriate, broken down or classified while still in a plastic state.

In the preparations produced in accordance with the invention, the active compound carbochromene hydrochloride is, surprisingly, also protected against hydrolytic decomposition caused by moisture and heat, so that preparations for the tropics can be packed in normal tropical packings.

Example 1.

Carbochromene hydrochloride	1,500 kg,
polyethylene glycol 6,000	0.332 kg,
HOECHST Wax E	0.168 kg,
calcium hydrogen phosphate	0.140 kg,
Aerosil 200	0.066 kg, and
methylhydroxyethylcellulose 1,000 cP	0.066 kg,

in a high-speed, closed mixer (HENSCHEL FM 10 L FLUID-Mixer equipped with a single-level exchangeable implement), were heated by mixing at 3,600 revolutions/minute, as a result of the friction produced, until granules of approx. 0.5—2 mm particle size were formed at approx. +70°C. While cooling, the granules were broken down on a vibratory sieve machine while in the phase in which they were still plastic.

0.082 kg of sodium amylopectin glycollate, 0.008 kg of Aerosil 200 and 0.038 kg of magnesium stearate were admixed with the cooled granules. This mixture was put into hard gelatin capsules or pressed into tablets or cores for film-coated tablets or dragées.

The dissolution characteristics *in vitro* (SARTORIUS model dissolver; "Sartorius" is a registered Trade Mark) for 1 hard gelatin capsule containing 150 mg of carbochromene hydrochloride and for 1 dragée containing 150 mg of carbochromene hydrochloride are shown in Table 2 compared with the soft gelatin capsules hitherto customary.

The stability under tropical conditions is shown in Table 1, compared with the forms for administration hitherto customary.

Example 2.

Carbochromene hydrochloride	450 g,
HOECHST Wax E	150 g,
calcium hydrogen phosphate	130 g,
hydrogenated castor oil	50 g,
Aerosil 200	5 g, and
methylhydroxyethylcellulose 1,000 cP	5 g,

were mixed in a slow-speed forced-flow mixer with a heated jacket (a MG 5 LÖDIGE mixer/jacket temperature approx. +90°C) until granules of particle size 0.5—2 mm were formed.

While cooling, the granules were broken down on an oscillating sieve. 10 g of magnesium stearate were admixed and oblong tablets with a weight of 800 mg were pressed and coated with a rapidly soluble aromatised film lacquer.

The dissolution characteristics *in vitro* (SARTORIUS model dissolver) for 1 film tablet containing 450 mg of carbochromene hydrochloride is shown in Table 2, compared with the soft gelatin capsules hitherto customary.

The stability under tropical conditions is shown in Table 1, compared with the forms for administration hitherto customary.

Example 3.

Carbochromene hydrochloride	9.000 kg,
Hoechst Wax E	3.667 kg,
calcium hydrogen phosphate	2.500 kg,
polyethylene glycol 6,000	0.333 kg,
Aerosil 200	0.100 kg, and
sodium carboxymethylcellulose 1,000 cP	0.100 kg,

in a high-speed, closed mixer (HENSCHEL FM 75 L FLUID-Mixer equipped with a two-level exchangeable implement), were heated by mixing, as a result of the friction produced, until granules of approx. 0.5—2 mm particle size were formed at approx. +70°C. While cooling, the granules were broken down on a vibrating sieve.

0.100 kg of Aerosil 200 and 0.200 kg of magnesium stearate were admixed with the cooled granules and oblong tablets with a weight of 800 mg were pressed and coated with a rapidly soluble aromatised-lacquer film.

The dissolution characteristics *in vitro* (SARTORIUS model dissolver) for 1 film tablet containing 450 mg of carbochromene hydrochloride is shown in Table 2.

Example 4.

Carbochromene hydrochloride	750.0 g,
Nifenalol HCl	500.0 g,
Hydroxycin 2 HCl	50.0 g,
polyethylene glycol 6,000	250.0 g,
HOECHST Wax E	125.0 g,
calcium hydrogen phosphate	75.0 g,
Aerosil 200	50.0 g,
	and
methylhydroxyethylcellulose 1,000 cP	50.0 g,

were mixed in a slow-running closed planetary mixer equipped with wipers and a heated jacket (MULTIHOMO MH 10 C/jacket temperature approx. +90°C) until granules of approx. 0.5—2 mm particle size were formed with the charge at approx. 70°C.

While cooling, the granules were broken down on a vibrating sieve. 54.0 g of maize starch, 25.0 g of Aerosil 200, 8.5 g of sodium amylopectin glycollate and 62.5 g of magnesium stearate were admixed and the product was pressed into dragée cores.

Example 5.

The homogeneous mixture resulting from grinding 0.050 kg of digoxin with 0.950 kg of calcium hydrogen phosphate was mixed with

polyethylene glycol 6,000	6.640 kg,
HOECHST Wax E	3.360 kg,
calcium hydrogen phosphate	1.800 kg,
Aerosil 200	1.320 kg,
	and
sodium carboxymethylcellulose 1,000 cP	1.320 kg,

and with carbochromene hydrochloride 30.000 kg in a slow-running, closed mixer with wipers and a heated jacket (DRAIS FH 165 planetary stirrer/jacket temperature approx. +90°C) until granules of 0.5 to 2 mm particle size were formed.

While cooling, the granules were broken down on a vibrating sieve. 1.640 kg of sodium carboxymethyl starch, 0.160 kg of Aerosil 200 and 0.760 kg of magnesium stearate were admixed, and the product was pressed into dragée cores.

Example 6.

The composition and the mode of operation corerspond to those of Example 5, but, instead of HOECHST Wax E, equal quantities of carnauba wax or hydrogenated castor oil or glyceryl mono/di/tri-stearate/palmitate were used. The resulting granules, of 0.5—2 mm particle size, were used further without being broken down.

Example 7.

The compositions and modes of operation correspond to those of Examples 1—6, but, instead of calcium hydrogen phosphate, the active compounds digoxin, α-methyldigoxin and dihydroergotamine tartrate, ground with calcium hydrogen phosphate, were used.

The SARTORIUS model dissolver is described in Pharm. Ind., *31* 794—799, and Pharm. Ind., *33*, 446—454.

TABLE 1

Stability (6 month's storage under tropical conditions, 40°C and 90% relative humidity)

Form for administration	External appearance	% hydrolysis product (acid formed by hydrolysis)
Carbochromene hydrochloride Soft gelatin capsules	spoiled	5–10%
Carbochromene hydrochloride Dragée/alcohol granules	spoiled	5–10%
Example 1 Dragée	stable	<2%
Example 2 Film tablet	stable	< 2%

TABLE 2

Release of active compound (SARTORIUS model dissolver) (in minutes)

% of active substance released after :

Form for administration	5'	10'	15'	30'	45'	60'	120'	180'	240'	300'	360'
Carbochromene hydrochloride Soft gelatin capsules	4	66	99								
Example 1 Hard gelatin capsules	29	95									
Example 1 Dragée	4	20	44	81	98						
Example 2 Film tablets				21	28	33	52	66	76	87	96
Example 3 Film tablet			11	19	26	32	66	87	98		

WHAT WE CLAIM IS:—

1. Process for the production of a solid preparation containing carbochromene hydrochloride, wherein carbochromene hydrochloride together with, based on the weight of the carbochromene hydrochloride, 1—30% by weight of filler, 1—20% by weight of swelling and disintegrating agent, 1—10% by weight of flowing and loosening agent, and 10—50% by weight of melting aid are submitted to heating and to intermixing, at a temperature in the softening range or melting range of the melting aid, until granules are formed therefrom.

2. Process according to Claim 1, wherein 2—20% by weight of filler are used.

3. Process according to Claim 1 or 2, wherein 2—10% by weight of swelling and disintegrating agent are used.

4. Process according to Claim 1, 2 or 3, wherein 2—8% by weight of flowing and loosening agent are used.

5. Process according to Claim 1, 2, 3 or 4, wherein 15—30% by weight of melting aid are used.

6. Process according to any of Claims 1 to 5, wherein the heating is achieved in a mixer by frictional heat.

7. Process according to any of Claims 1 to 5, wherein the heating is achieved in a mixer by means of a heated surface.

8. Process according to any of Claims 1 to 7, wherein the agglomerated granules initially formed are broken down.

9. Process according to any of Claims 1 to 8, wherein 1—15% by weight of flowing and loosening agent and/or mould release agent and lubricant are admixed with the granules.

10. Process according to any of Claims 1 to 9, wherein 2—10% by weight of flowing and loosening agent and/or mould release agent and lubricant are admixed with the granules.

11. Process according to any of Claims 1 to 10, wherein a polyethylene glycol is used as the melting aid.

12. Process according to any of Claims 1 to 11, wherein a colloidally dispersed or amorphous silicic acid is used as the flowing and loosening agent.

13. Process according to any of Claims 1 to 12, wherein starch, sodium amylopectin glycollate, sodium carboxymethyl starch, or crosslined polyvinylpyrrolidone is used as the swelling and disintegrating agent.

14. Process according to any of Claims 1 to 10, wherein a montan wax acid, a montan wax acid ester, carnauba wax or glyceryl mono/di/tri-stearate/palimtate is used as the melting aid.

15. Process according to any of Claims 1 to 10, wherein colloidally dispersed hydrophobic silicic acid is used as the flowing and loosening agent.

16. Process according to any of Claims 1 to 10, wherein a sodium carboxymethylcellulose, methylcellulose, methylhydroxyethylcellulose or hydroxypropylmethylcellulose is used as the swelling and disintegrating agent.

17. Process according to claim 1, substantially as described in any of the foregoing Examples.

18. A solid preparation containing carbochromene hydrochloride, produced by a process according to any of the preceding claims.

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